nature reviews disease primers

https://doi.org/10.1038/s41572-024-00563-5

Primer

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Metabolic syndrome

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Abstract

The metabolic syndrome (MetS) is a multiplex modifiable risk factor for cardiovascular disease, type 2 diabetes mellitus and other health outcomes, and is a major challenge to clinical practice and public health. The rising global prevalence of MetS, driven by urbanization, sedentary lifestyles and dietary changes, underlines the urgency of addressing this syndrome. We explore the complex underlying mechanisms, including genetic predisposition, insulin resistance, accumulation of dysfunctional adipose tissue and ectopic lipids in abdominal obesity, systemic inflammation and dyslipidaemia, and how they contribute to the clinical manifestations of MetS. Diagnostic approaches vary but commonly focus on abdominal obesity (assessed using waist circumference), hyperglycaemia, dyslipidaemia and hypertension, highlighting the need for population-specific and phenotype-specific diagnostic strategies. Management of MetS prioritizes lifestyle modifications, such as healthy dietary patterns, physical activity and management of excess visceral and ectopic adiposity, as foundational interventions. We also discuss emerging therapies, including new pharmacological treatments and surgical options, providing a forward-looking perspective on MetS research and care. This Primer aims to inform clinicians, researchers and policymakers about MetS complexities, advocating for a cohesive, patient-centred management and prevention strategy. Emphasizing the multifactorial nature of MetS, this Primer calls for integrated public health efforts, personalized care and innovative research to address this escalating health issue.

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Introduction

The metabolic syndrome (MetS) is an established conceptual framework that links several distinct, albeit interrelated, risk factors for cardiovascular diseases (CVDs) to a defined, measurable syndrome associated with increased risk of CVD[1–3]. The connection between excess adiposity, diabetes mellitus and hypertension was first introduced by the Framingham Heart Study in the 1960s. Yet the late Gerald Reaven first proposed in 1988, the revolutionary concept that premature CVD is frequently caused by a cluster of prevalent abnormalities that include a high triglyceride–low HDL cholesterol state of dyslipidaemia, hypertension and insulin resistance (IR)[4], initially referred to as 'syndrome X'. A major advance underlying this concept was the recognition that this cluster of abnormalities is associated with increased CVD risk even in the absence of hyperglycaemia or type 2 diabetes mellitus (T2DM). The public health and clinical implications were obvious: individuals at increased risk of premature CVD could be detected early and prescribed preventive interventions, even before the development of hyperglycaemia and T2DM.

As the term syndrome X was used in cardiology to describe another condition, 'IR syndrome' became increasingly used as an alternative name in the literature. Several high-profile organizations then proposed tools to identify individuals with features of the IR syndrome, such as the WHO in 1998 (ref. 5) and the European Group for the Study of Insulin Resistance in 1999 (ref. 6). However, some of the measurements proposed (for example, serum concentration of insulin) were not always available to many health-care practitioners.

Thus, in 2001, the National Cholesterol Education Program–Third Adult Treatment Panel (NCEP-ATP III) committee proposed simple clinical markers and cut-off values that could be used in primary care to identify individuals who are likely to be characterized by the features of the IR syndrome[7]. Abdominal obesity, particularly visceral obesity (excess adipose tissue accumulation inside the abdominal cavity), was well documented as a frequent comorbid condition of the IR syndrome, if not its most prevalent form by far[8]. Hence, the committee proposed the use of waist circumference (WC) as a crude index of abdominal obesity, along with four other simple markers: fasting serum levels of triglycerides and HDL cholesterol, blood pressure and fasting glycaemia. As no measurement of insulin or IR was used in the NCEP-ATP III diagnosis approach, the term 'the metabolic syndrome' was proposed to describe this constellation of interrelated abnormalities[7]. On the basis of the relationship with clinical outcomes, the presence of at least three out of the five criteria was suggested to enable the diagnosis of MetS, as all combinations seemed to predict an increased risk of CVD[9]. Subsequently, in 2009, specific WC cut-off values for abdominal obesity for various populations were proposed by the International Diabetes Federation (IDF) that were dependent on sex, country or race/ethnicity[10].

Since these landmark publications, more than 150,000 items have been published using 'the metabolic syndrome', as found on Web of science. Despite the importance of this constellation of metabolic abnormalities for clinical practice and population health, the concept has been the topic of many debates and controversies regarding its pathophysiology and clinical diagnosis, as well as its questionable use as a risk calculator or binary treatment outcome, not taking severity into account[11].

In 2023, the American Heart Association (AHA) expanded the concept of MetS into cardiovascular–kidney–metabolic (CKM) syndrome, to improve the diagnosis and management of patients through various stages of metabolic, cardiovascular and kidney dysfunction[12]. This expanded concept addresses the pathophysiological interrelationship among CVD, chronic kidney disease (CKD) and metabolic disorders. CKM syndrome highlights the convergence of cardiovascular, kidney and metabolic risk factors contributing to adverse outcomes in both cardiovascular and renal health.

The aim of this Primer is to familiarize the reader with a broad overview and update on MetS, covering epidemiology, pathophysiology, the link to clinical outcomes, diagnosis and screening, prevention and managing patients with MetS. Progress made in linking MetS to clinical outcomes other than CVD is also highlighted. Furthermore, gaps in current knowledge and future research perspectives relevant to clinical practice and population health strategies are discussed.

Epidemiology

MetS definition

The WHO proposed an initial working definition for IR syndrome in 1998 (ref. 5). Since then, various criteria have been proposed for the clinical diagnosis of MetS. Among these, the NCEP-ATP III definition has been the most widely utilized[7]. In 2005, the IDF introduced a new, globally applicable definition of MetS[13], emphasizing abdominal obesity as a crucial component, which must be assessed using race/ethnicity-specific and sex-specific cut-off values for WC. Additionally, the American Association of Clinical Endocrinologists[14] and the AHA/National Heart, Lung, and Blood Institute (AHA/NHLBI)[15] have each proposed their own definitions. In 2009, a collaborative statement from the IDF, AHA/NHLBI, the World Heart Federation, the International Atherosclerosis Society and the International Association for the Study of Obesity introduced 'harmonized' criteria for MetS[10] (Table 1).

The global prevalence of MetS in adults

Prevalence in the Americas and Europe. In North America, particularly in the USA, the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018 revealed a troubling increase in the prevalence of MetS[16]. The total prevalence of MetS in the USA using the NCEP-ATP III definition rose from 37.6% in 2011–2012 to 41.8% in 2017–2018. This rise is partly attributable to a population-level increase in elevated blood glucose levels, indicative of a growing epidemic of T2DM. The trend is more pronounced among participants with low educational attainment, highlighting the effect of socioeconomic status on MetS prevalence. The NHANES data underscore the need for lifestyle modifications and targeted interventions to manage MetS effectively, particularly in socioeconomically disadvantaged groups.

In Canada, the prevalence of MetS among adults using the harmonized definition of 2009 is estimated at 41.9%[17]. This study found that the risk of developing MetS was significantly lower among women than among men. Socioeconomic factors, particularly material deprivation, have also been linked to increased MetS risk. Women were found to be the most socially deprived, indicating the need for sex-specific and gender-specific public health strategies in Canada. In Mexico, a study involving 6,567 adults (mean ± s.d. of age: 37.9 ± 11.4 years for men and 38.2 ± 10.8 years for women), showed that 28.9% of men and 44.4% of women are affected by MetS (defined using the IDF harmonized definition), a notably higher prevalence in women than in men[18]. Particularly, abdominal obesity and low HDL cholesterol components were more prevalent in women than in men in this study. Contributing factors included genetic predisposition, consumption of a high carbohydrate diet, sedentary lifestyle and inadequate public health policies aimed at reducing the effects of MetS. This high prevalence of MetS in these

Table 1 | Diagnostic criteria proposed for the clinical diagnosis of MetS by professional organizations

Organization (year)	MetS definition	Insulin resistance or hyperglycaemia	Adiposity	Dyslipidaemia	Elevated blood pressure	Other
WHO (1998)[5]	Insulin resistance plus any other two criteria	Impaired glucose regulation or diabetes mellitus, or lowered insulin sensitivity	Waist-to-hip ratio >0.90 in men, waist-to-hip ratio >0.85 in women and/or BMI >30 kg/m^2	TGs ≥150 mg/dl (1.69 mmol/l) and/or HDL-C <35 mg/dl (0.91 mmol/l) in men or <39 mg/dl (1.01 mmol/l) in women	≥140/90 mmHg	Microalbuminuria (≥20 µg per min or albumin-to-creatinine ratio ≥20 mg/g)
EGIR (1999)[6]	Insulin resistance plus any other two criteria	Plasma insulin >75th percentile, impaired glucose tolerance, or impaired fasting glucose	WC ≥94 cm in men or ≥80 cm in women	TGs ≥150 mg/dl (1.69 mmol/l) and/or HDL-C <39 mg/dl (1.01 mmol/l) in men or women	≥140/90 mmHg or on hypertension therapy	None
ATP III (2001)[7]	Any three of five criteria	Fasting plasma glucose >110 mg/dl (6.11 mmol/l), which was modified in 2004 to >100 mg/dl (5.55 mmol/l), or diabetes mellitus	WC ≥102 cm in men or ≥88 cm in women	TGs ≥150 mg/dl (1.69 mmol/l), HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women	≥130/85 mmHg	None
AACE (2003)[138]	Insulin resistance plus any other two criteria	Impaired glucose tolerance or impaired fasting glucose (but not diabetes mellitus)	BMI ≥25 kg/m^2	TGs ≥150 mg/dl (1.69 mmol/l) and HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women	≥130/85 mmHg	Other features of insulin resistance including family history of diabetes mellitus, PCOS or sedentary lifestyle
IDF (2005)[13]	Body weight plus any other two criteria	Fasting plasma glucose >100 mg/dl (5.55 mmol/l), diabetes mellitus	Increased WC (population-specific)	TGs ≥150 mg/dl (1.69 mmol/l) or on therapy, HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women or on lipid-lowering therapy	≥130/85 mmHg or on hypertension therapy	None
AHA/NHLBI (2005)[15]	Any three of five criteria	Fasting plasma glucose >100 mg/dl (5.55 mmol/l) or on antihyperglycaemic therapy	WC ≥102 cm in men or ≥88 cm in women	TGs ≥150 mg/dl (1.69 mmol/l) or on therapy, HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women or on lipid-lowering therapy	≥130/85 mmHg or on hypertension therapy	None
Joint Scientific Statement from IDF, NHLBI, AHA, WHF, IAS and IASO (2009)[10]	Any three of five criteria	Fasting plasma glucose >100 mg/dl (5.55 mmol/l) or on antihyperglycaemic therapy	Population-specific and country-specific definitions (see 'Other' cell)	TGs ≥150 mg/dl (1.69 mmol/l) or on lipid-lowering therapy, HDL-C <40 mg/dl (1.03 mmol/l) in men or <50 mg/dl (1.29 mmol/l) in women or on therapy	≥130/85 mmHg or on hypertension therapy	Recommended that the IDF cut points be used for people who are not of European origin and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available

AACE, American Association of Clinical Endocrinologists; AHA, American Heart Association; ATP III, National Cholesterol Education Program's Adult Treatment Panel III; EGIR, European Group for the Study of Insulin Resistance; HDL-C, HDL cholesterol; IAS, International Atherosclerosis Society; IASO, International Association for the Study of Obesity; IDF, International Diabetes Federation; MetS, the metabolic syndrome; NHLBI, National Heart, Lung, and Blood Institute; PCOS, polycystic ovary syndrome; TGs, triglycerides; WC, waist circumference; WHF, World Health Federation; WHO, World Health Organization. Adapted with permission from ref. 11, Elsevier.

regions is alarming and calls for urgent public health strategies to address the multifactorial components contributing to MetS.

The MORGAM Project analysed data from 26 European cohorts and included 69,094 men and women aged 19–78 years, with baseline measurements taken between 1982 and 1997. In this study, the prevalence of MetS was higher using the NCEP-ATP III criteria than using the IDF criteria: 19.9% versus 9.7% in men and 32.1% versus 29.5% in women[19]. Another important European study, the UK Biobank, involved over 308,000 participants and identified 75,486 individuals (24.5%) with MetS, with a higher proportion being women (53.4%) and a mean age of 56.4 years[20]. Notably, MetS was associated with a 13.6% increased risk of anxiety over a mean follow-up period of 12.1 years, with certain inflammatory parameters such as C-reactive protein and leukocyte count mediating this relationship[20].

Prevalence in Asia

MetS is a growing problem in Asia. In Japan, a large cohort study focused on the association between MetS and CVD, emphasizing the importance

of WC and sex-specific criteria in MetS diagnosis[21]. The prevalence of MetS varied: 11.9% among men and 8.4% among women using the IDF definition and 17.9% among men and 9.2% among women using a modified NCEP-ATP III definition. This study highlights the importance of specific diagnostic criteria for MetS, as well as the need for sex-specific and race/ethnicity-specific approaches in managing this condition.

South Korea has experienced a considerable increase in MetS prevalence, with age-adjusted prevalence rising from 27.1% in 2001 to 33.2% in 2020 (ref. 22). This increase was driven by increased MetS in men, with a marked difference in MetS prevalence between men (25.8% increasing to 40.0%) and women (28.2% decreasing to 26.2%). Key contributors to this trend were high serum levels of glucose and large WC, which have been increasing steadily over the past 20 years. The population proportion with a high serum glucose level and large WC has increased substantially by 17.9% and 12.2% over 20 years, respectively. By contrast, circulating HDL cholesterol levels increased notably, resulting in a 20.4% decrease in the proportion of individuals with low HDL cholesterol. Notable dietary shifts (for example, decreases in carbohydrate intake and increases in fat consumption) and large decreases in physical activity induced by the excessive use of electronic devices seem to be key factors for the evolving features of MetS in South Korea.

In China, MetS is becoming an increasingly important health issue[23]. Of the 77,639 participants enrolled in the China Multi-Ethnic Cohort (mean age 50.2 ± 11.1 years, 39.0% men), the prevalence of MetS was 19.4% and varied across demographic subgroups: 31.0% in men, 17.0% in women; 24.2% in those aged ≥60 years and 18.1% in those aged <60 years. The study of Chinese populations reveals a complex interplay of lifestyles, dietary habits and genetic factors, in the prevalence and manifestation of MetS.

In a 2003 study involving 475 Indian individuals aged 20–75 years from a population database, the prevalence of MetS was 41.1% using the NCEP-ATP III criteria with modified WC cut-off values (men ≥90 cm, women ≥85 cm)[24]. In a meta-analysis published in 2020 that included 111 studies, with a total of 133,926 Indian adults, the prevalence of MetS was 30% (95% CI 28–33%) using either the NCEP-ATP III or IDF definitions (WC criteria: men ≥102 cm, women ≥88 cm)[25]. Region/country and ethnicity-specific cut-off points of BMI and WC for defining overweight, obesity and abdominal obesity are presented in Table 2.

Table 2 | Region/country and ethnicity-specific cut-off values for BMI and WC thresholds for abdominal obesity

Country or region	BMI (kg/m^2)		WC (cm)	
	Obesity	Overweight	Men	Women
Most countries in North America and Europe[221]	30.0	25.0	102	88
Asia[3]				
China[222]	28.0	24.0	90	85
Malaysia[223]	27.5	23.0	90	80
Singapore[223]	27.5	23.0	90	80
Taiwan[224]	27.0	24.0	90	80
India[225]	25.0	23.0	90	80
Japan[226]	25.0	–	85	90
Republic of Korea[227]	25.0	23.0	90	85
Philippines[223]	25.0	23.0	90	80
Sri Lanka[223]	25.0	23.0	90	80
Hong Kong, SAR[228]	25.0	23.0	90	80
Bangladesh[223]	25.0	23.0	90	80
Thailand[223]	25.0	23.0	90	80
Vietnam[223]	25.0	23.0	90	80
Other countries/regions or ethnicities				
Māori and Pacific Islanders[229]	32.0	26.0	102	88
Tunisia	–	–	85	85
Iran	–	–	89	91
Sub-Saharan Africa	–	–	94	80
Eastern Mediterranean and Middle East	–	–	94	80

Waist circumference (WC) cut-off values that correlate with health risks owing to excess abdominal adiposity can vary by ethnicity. For example, South Asian individuals tend to accumulate abdominal adiposity, which is linked to increased health risks such as type 2 diabetes mellitus, at lower WC values compared with other ethnic groups[230–232].

Prevalence in Africa

MetS is also an emerging problem in Africa. In a study from 29 African countries and involving 156,464 participants, the overall prevalence of MetS in Africa was 32.4% (95% CI 30.2–34.7%) with significant heterogeneity (I^2 = 98.9%; P < 0.001)[26]. In particular, MetS poses considerable social and clinical challenges for individuals living with HIV in Africa[27]. In a pooled analysis including 24 studies, the prevalence of MetS was found to be 21.01% (95% CI 16.5–25.5%) by the NCEP-ATP III criteria. Low HDL cholesterol was the highest prevalent component (47.3%), followed by abdominal obesity (38.4%)[27]. Thus, MetS in this region presents unique challenges due to the diverse socioeconomic and health landscapes across the African continent. Tailored public health strategies and interventions will be required, which consider the specific regional and cultural contexts.

The global prevalence of MetS among children and adolescents

Notably, no established consensus exists on the definition of MetS in children and adolescents[28]. The most widely used definitions are the IDF definition and the NCEP-ATP III criteria modified for age[29,30], both of which incorporate age-specific and sex-specific WC percentiles for abdominal obesity and percentiles for height-specific systolic and diastolic blood pressure. Several proposed definitions are presented in Supplementary Table 1. The development of a standardized definition for MetS in this age group is imperative to ensure accurate diagnosis and effective management.

The prevalence of MetS among children and adolescents reveals substantial differences and trends specific to each country. In the USA, a study utilizing data from NHANES between 2001 and 2020 found the estimated prevalence of MetS in adolescents to be 2.66%[31]. The prevalence was slightly higher in adolescents from food-insecure households (3.39%) compared with those from food-secure households (2.48%). Hispanic adolescents had the highest prevalence at 3.73%. Over the past two decades, the prevalence of MetS has remained below 5%, showing no significant time trend[31]. The study suggested that food-insecure household status might contribute to the risk of MetS.

In South Korea, the prevalence of MetS among adolescents increased notably during the COVID-19 pandemic, according to data from the Korean National Health and Nutrition Examination Surveys

conducted in 2019–2020. The overall prevalence of MetS in adolescents rose from 3.79% to 7.79% during this period[32]. Considerable changes were observed in components of MetS, such as diastolic blood pressure, serum triglyceride levels and HDL cholesterol levels. The study also highlighted an increase in severe obesity, which was defined by ≥99th percentile of BMI for sex and age, and abdominal obesity, particularly among boys aged 10–18 years.

In India, a systematic review and meta-analysis of 16 studies involving 19,044 adolescents showed a pooled prevalence of MetS of 3.4% using IDF criteria and 5.0% using the NCEP-ATP III criteria[33]. The study noted a higher prevalence of MetS in urban areas, and found that MetS occurrence was linked to factors such as urbanization, sedentary lifestyles and dietary changes. According to the China National Nutrition and Health Surveillance data 2016–2017 (n = 58,712), the prevalence of MetS by the revised definition of NCEP-ATP III[34] was 5.45% among students aged 7–17 years[35]. Intriguingly, a high level of screen time was significantly associated with MetS in this age group. Thus, the prevalence of MetS in children and adolescents is also at a concerning level and might increase rapidly in the future.

Summary

These reports detailing the characteristics of MetS across diverse global regions underscore its complex nature, shaped by a confluence of genetic, lifestyle and socioeconomic influences. Robust public health strategies need to be implemented to address the observed increase in MetS prevalence globally. These strategies should focus on promoting healthy lifestyles and enhancing health-care accessibility. Notably, the prevalence of MetS among adolescents is marked by distinct variations across different countries, each characterized by unique trends and contributory factors. Collectively, these findings highlight the critical importance of early detection and lifestyle interventions in the prevention of MetS and its associated complications.

Mechanisms/pathophysiology

Visceral adipose tissue and ectopic fat

Adipose tissue is an endocrine tissue that stores excess lipids and expands via two mechanisms: either the existing adipocytes increase in size (hypertrophy) or the number of adipocytes increases (adipogenesis, otherwise known as hyperplasia). One of the predictors and cardinal indicators of disease in individuals with overweight or obesity is the presence of excess visceral adipose tissue (VAT), defined as an accumulation of hypertrophic adipose tissue within the abdomen, on abdominal structures such as the greater omentum and mesentery[36,37]. This feature is frequently accompanied by excess ectopic accumulation of triglycerides in the liver[38,39], muscle[40,41], pancreas[42], renal sinus and/or perinephric space[43], or as intrapericardial[44,45] and extrapericardial (that is, mediastinal) adipose tissue[46], or intramyocardial triglycerides[47,48]. The preferential accumulation of VAT is now recognized as a marker of adipose tissue dysfunction in other body sites used for lipid storage, including peripheral and more centrally located subcutaneous adipose tissue (SAT) compartments (reviewed in refs. 36,49).

Adipose tissue dysfunction is now emerging as one of the main drivers and aetiological factors for MetS. This dysfunction includes many features, such as adipocyte hypertrophy, impaired adipogenesis, resistance to the inhibitory effect of insulin on lipolysis and low free fatty acid (FFA) uptake, reduced triglyceride synthesis, excess collagen deposition, impaired extracellular matrix remodelling, immune cell infiltration and inflammatory cytokine secretion, as well as altered vascular architecture and remodelling[36,50–56].

Genetics. Susceptibility to visceral storage of adipose tissue is determined in part by genetics, first demonstrated in overfeeding studies of monozygotic twins over three decades ago[57]. Several studies using Mendelian randomization have since demonstrated associations between genetic variants that are associated with MetS and its components, and adverse health outcomes, such as coronary artery disease[58], stroke[59], cancer[60] and even psychiatric disorders[61]. Genetic susceptibility to MetS has been previously reviewed[62] and might be related to several genetic polymorphisms including: *LDLR*, *GBE1*, *Il1R1*, *TGFB1*, *Il6*, *COL5A2*, *SELE* and *LIPC* (P values range from 0.047 to 0.008)[63]. Variants in seven additional genes show significant gene interaction by sex.

Sex differences. Sex-based differences in VAT and MetS could also relate to higher circulating levels of oestrogens and lower levels of testosterone in women than in men[64,65]. An increase in body adiposity combined with a changed distribution of adipose tissue depots to a more central, abdominal distribution can be observed in postmenopausal women, and these effects could be mediated by ovarian hormone changes[66]. Accretion of visceral adiposity in women after menopause has been postulated as a cause for the increased cardiovascular risk seen during this stage of life in women. Furthermore, the notable correlation between the *PNPLA3* p.I148M variant and metabolic dysfunction-associated steatotic liver disease (MASLD; previously called non-alcoholic fatty liver disease) and metabolic dysfunction-associated steatohepatitis (MASH) has been shown to be stronger in postmenopausal women than in men[67], with a stronger correlation with visceral adiposity relative to that in men[64]. This increased susceptibility to hepatic accumulation of lipids among postmenopausal women was attributed to the deteriorated insulin sensitivity and changes in adiposity that occur with blunted oestrogen secretion, which generate blunted upregulation of hepatic PNPLA3 via the oestrogen receptor[64,67].

Ectopic lipid deposition. MetS disease risk tracks closely with VAT and ectopic (for example, cardiac) lipid and adipose tissue accumulation[48] as well as with hepatic steatosis and with MASLD. The risk of disease does not necessarily reflect the size of the body adipose tissue depots, but the functional ability of adipose tissues to efficiently manage daily lipid fluxes[68].

Among the ectopic adipose tissue depots, epicardial adipose tissue (lipid deposition in the epicardium) has been well studied[69]. Epicardial adipose tissue is associated with clinical and subclinical atherosclerosis[70,71], and fatty infiltration in the myocardium resulting in abnormal diastolic function[72] and elevated risk of arrhythmia[73], via the secretion of pro-inflammatory cytokines with paracrine and vasocrine effects. Increasing evidence also indicates an association between perinephric adipose tissue, which is located adjacent to the kidney in the retroperitoneal area, and increased risk of MetS, hypertension and adverse cardiovascular and/or kidney outcomes[74,75]. In addition, adipose tissue dysfunction also leads to spillover of non-esterified fatty acids from adipose tissue into the circulation during the postprandial phase, reflecting paradoxically impaired triglyceride synthesis[76]. This condition probably also results from impaired insulin signalling in adipose tissue, which leads to blunted inhibition of lipolysis[76,77]. Impaired adipose tissue triglyceride synthesis and fatty acid spillover contribute to longer transient postprandial rises in serum triglyceride levels, a phenomenon closely linked to IR[78] and ectopic lipid accumulation in various tissues and organs (reviewed in ref. 79).

Adipogenesis or hypertrophy? For a very similar total body adiposity, VAT accumulation can be highly variable, even in the presence of normal BMI values (Fig. 1). In the presence of overnutrition and a positive energy imbalance, adipose tissue expansion takes place through triglyceride synthesis in existing adipocytes, which leads to cell hypertrophy, as well as the recruitment and adipogenic differentiation of precursor cells into new mature, lipid-storing cells (adipogenesis)[80]. The ability to generate new adipocytes through adipogenesis is highly variable. We now know from animal models of impaired adipogenesis or studies in individuals with lipodystrophy (a disorder of complete or partial loss, and/or abnormal distribution of adipose tissue) that impaired adipogenesis is a key factor for the development of cardiometabolic complications (reviewed in ref. 81) and that this phenomenon quite logically coincides with hypertrophy of existing adipocytes[82].

Excess accumulation of VAT clearly relates to hypertrophy of visceral adipocytes (Fig. 1). Such hypertrophy could reflect limited VAT storage capacity as well as low adipogenic capacity in other adipose tissue compartments, including SAT. Limited storage capacity of certain adipose tissue depots could mediate hormonal effects leading to sex-specific adipose tissue accumulation patterns, but also adipose tissue dysfunction in the case of chronic overnutrition[83]. Accordingly, in a study where adipogenic capacity was measured in vitro with cell fractions isolated from SAT and VAT biopsy samples obtained from women, the adipogenic potential of cells from the visceral compartment was not related to risk variables of the donors, such as fasting triglyceride levels and VLDL triglyceride content. Yet lower adipogenic potential of subcutaneous pre-adipocytes was related to increased triglyceride levels and higher lipid content in VLDLs, and most importantly, to adipocyte hypertrophy in the VAT compartment of these tissue donors[84].

Specific mechanisms leading to blunted adipogenesis in adipocyte precursor cells involve altered cell signalling through transcription factors such as PPARγ and C/EBPα, which are involved in maintaining the expression of the set of genes involved in mature adipocyte function. Treatment with PPARγ agonists (such as the insulin sensitizer thiazolidinedione, which has been used to manage blood glucose levels in patients with diabetes mellitus) improves glucose and lipid metabolism through the expansion of SAT (and decrease in VAT mass and hepatic steatosis)[85]. Additional signalling pathways are involved in adipogenesis, including WNT and factors such as VSTM2A and BMP4, which might have a role in early adipogenic differentiation[86]. Reports also show that progenitor cells not undergoing adipogenic differentiation might be senescent[87], with lower rates of adipogenic differentiation in VAT than in SAT[88], which relates to adipocyte hypertrophy, dyslipidaemia and IR[88,89].

MASLD

The new criteria for the diagnosis of MASLD are based on the presence of steatosis and one or more MetS components, in the absence of other causes for secondary hepatic lipid accumulation[90]. Although the new definition does not specifically mention MetS, it recognizes the importance of individual features of MetS in the development and progression of steatotic liver disease. The prevalence of MASLD is higher in individuals with MetS than in those without MetS[91] and increases with the number of MetS-defining criteria[92]. Those with MASLD often show alterations in their plasma lipid profile, with increased triglycerides due to high secretion of VLDL[93], especially in the presence of IR and increased VAT accumulation[94]. Moreover, individuals with MASLD have increased VAT accumulation, even when BMI is within the normal range, high adipose tissue IR and increased lipolysis[39], which trigger a spillover of FFAs to the liver, where they are used for the synthesis of triglycerides and are associated with elevated gluconeogenesis and hepatic glucose output[95], thereby increasing the risk of hyperglycaemia and T2DM (Fig. 2).

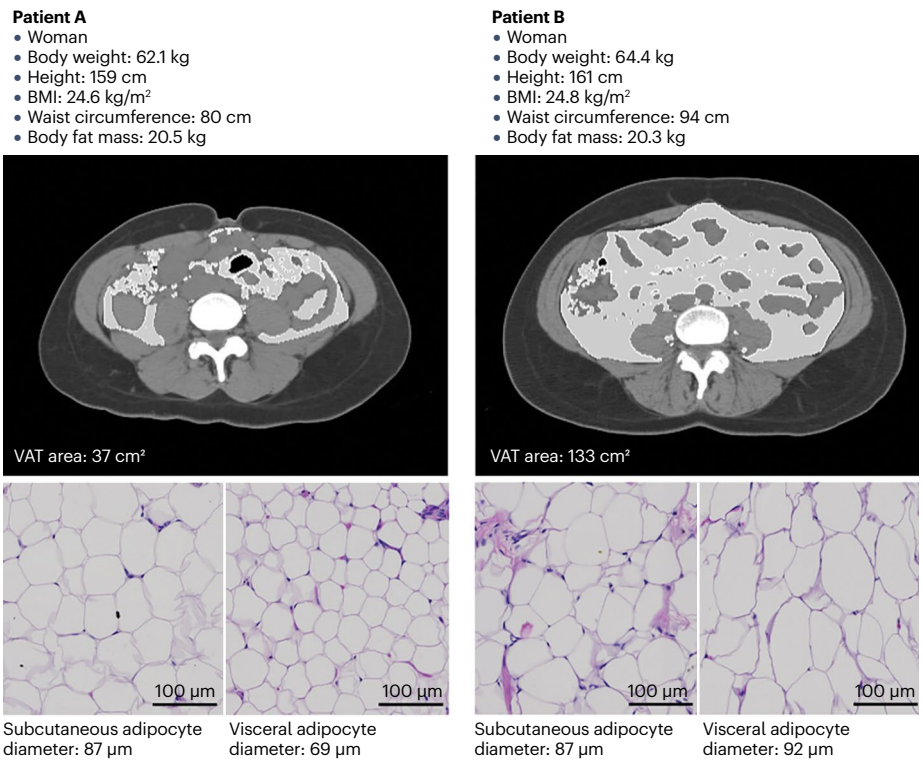

Fig. 1 | Adipose tissue characteristics can differ between individuals with similar BMI and total body fat mass. Anthropometric characteristics, CT scans and microscopic adipose tissue images in two women with similar BMI and total body fat mass values, but widely differing visceral adipose tissue (VAT) accumulation measured by CT. Total body fat mass was measured by whole-body dual energy absorptiometry. CT measurement of VAT was performed at the L4–L5 vertebrae level and the abdominal cavity was delineated using Image J software. Adipose tissue samples from patients A and B were obtained during gynaecological surgery. A portion of each adipose sample was fixed in formalin and stained with haematoxylin and eosin. Slides were visualized under a bright-field microscope. Representative images are shown (scale bars 100 µm). The average cell diameter was measured from 250 mature adipocytes in suspensions obtained from collagenase digestion of the remaining portion of each sample. Patient B has evidence of hypertrophic VAT.

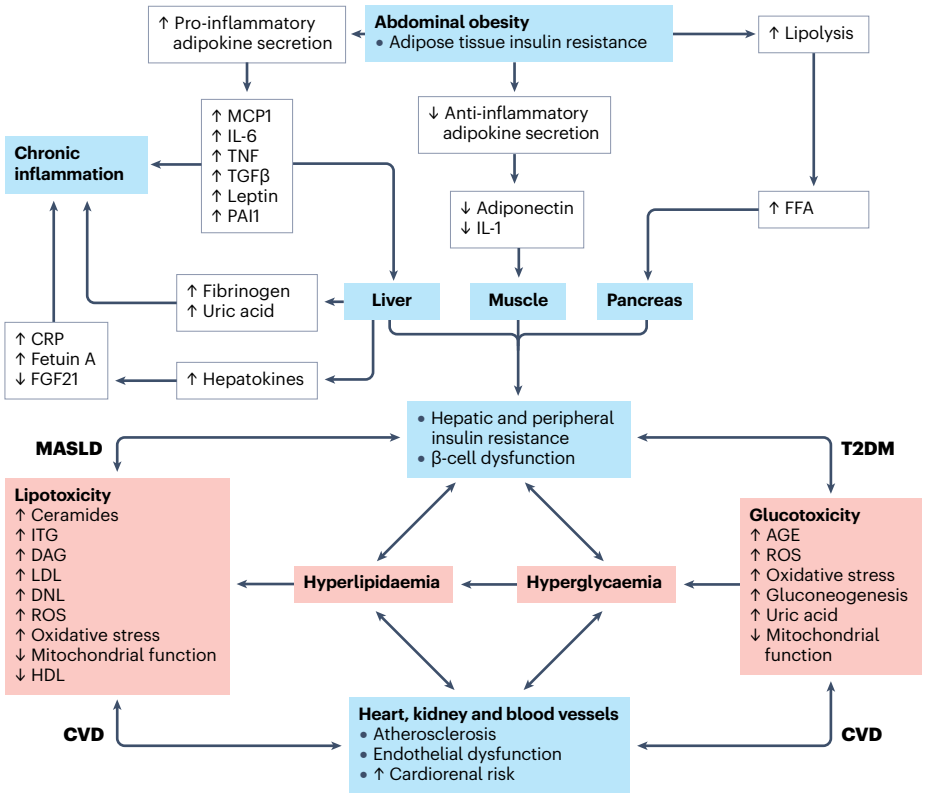

Fig. 2 | Molecular pathways involved in MetS. The visceral adipose tissue (VAT) that accumulates in abdominal obesity (with associated adipocyte hypertrophy and ectopic lipid deposition) is a highly active endocrine organ that contributes to a cascade of pathophysiological alterations that affect several organ systems, thereby leading to multiorgan dysfunction and ultimately cardiovascular–kidney–metabolic syndrome. VAT is highly lipolytic with increased free fatty acid (FFA) deposits in organs such as the liver, skeletal muscle and pancreas. Imbalance between increased pro-inflammatory cytokines and reduced anti-inflammatory cytokines leads to a state of chronic inflammation with pro-inflammatory, prothrombotic and pro-insulin resistance consequences. Metabolic dysfunction characterized by hepatic and peripheral insulin resistance results in lipotoxicity and glucotoxicity that increases the risk of multiorgan dysfunction (type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD)), and eventually cardiovascular dysfunction and increased risk of cardiovascular disease (CVD), such as atherosclerosis, heart failure, atrial fibrillation and kidney disease. AGE, advanced glycation end product; CRP, C-reactive protein; DAG, diacylglycerols; DNL, de novo lipogenesis; FGF21, fibroblast growth factor 21; ITG, intramyocardial triglyceride; MCP1, monocyte chemoattractant protein 1; MetS, the metabolic syndrome; PAI1, plasminogen activator inhibitor 1; ROS, reactive oxygen species; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

The liver secretes several hepatokines, such as C-reactive protein and fetuin A, and in the presence of steatosis and MASLD their synthesis and secretion are increased, whereas fibroblast growth factor 21 (FGF21) is decreased. Fetuin A was the first hepatokine proposed to regulate metabolic homeostasis through inter-organ crosstalk, and is an independent risk factor for the development of T2DM[96]. Moreover, serum levels of fetuin A are positively correlated with the degree of hepatic lipid content, IR and glucose intolerance[97], and increased fetuin A is a risk factor for CVD. Circulating FGF21 is secreted mainly by the liver and exerts metabolic and anti-inflammatory effects on multiple organs, including adipose tissue, pancreas, heart, kidney and brain, in a paracrine or endocrine manner by signalling via several FGF receptors and its co-receptor β-klotho[98].

The combination of high VAT accumulation and high liver lipid content is associated with an increase in IR in liver, muscle and adipose tissue[99]. Individuals with high VAT volume and a high degree of hepatic steatosis also have the highest prevalence of MetS, as shown in the Jackson Heart Study, a large cohort of African American women and men[91]. Similar results were confirmed in the Dallas Heart Study (a multiethnic, population-based study), in which high VAT mass and high degree of hepatic steatosis, and high VAT mass and a low degree of hepatic steatosis, were associated with increased risk of T2DM (OR 7.8 and 3.3, respectively)[100]. Interestingly, in this same study, excess hepatic lipid content combined with excess VAT mass was associated with increased CVD risk, whereas excess hepatic lipid content alone was not. In fact, excess VAT mass was associated with increased CVD risk with or without hepatic steatosis, and individuals with high VAT mass but low liver lipid content had the highest incidence of CVD events. All these factors could also explain the heterogeneity in the risk of incident CVD in those with MASLD, as shown in various studies including a meta-analysis[101] and a Mendelian randomization study[102].

Insulin resistance and inflammation

IR is central in the development of MetS and has been recognized from the beginning as the major determinant of cardiometabolic risk. Individuals with IR have impaired insulin action that affects glucose

metabolism in the muscle and liver, as well as FFA release from adipose tissue through reduced lipolysis inhibition. These effects are linked to high release or postprandial spillover of FFAs that are then taken up by peripheral tissues where, when in excess, they alter insulin signalling and action[103,104].

FFAs induce IR and decrease muscle ATP synthesis[105] and stimulate nitric oxide production as well as endothelial nitric oxide synthase[106]. Furthermore, IR impairs insulin-stimulated activation of PI3K, pyruvate dehydrogenase kinase, isozyme 1 and RACα serine–threonine protein kinase[106]. Reduced insulin sensitivity in muscle, adipose tissue and liver leads to high hepatic glucose production through activation of gluconeogenesis[107]. Both excessive glucose and FFA release are associated with increased oxidative stress, uncoupled oxidative phosphorylation, production of reactive oxygen species (ROS), formation of advanced glycated end-products, accumulation of toxic lipids such as diacylglycerols (DAG), ceramides and long-chain fatty acyl-CoA, which have been shown to promote inflammation and impair cellular metabolism[108]. Moreover, certain lipids, such as ceramides and DAGs, are linked to IR in muscle and liver[109–114] and when found in excess in the circulation, they are a marker of increased risk of CVD[115].

Inflammation is closely linked to IR and adipose tissue dysfunction through several mechanisms and is an important contributor to the pathophysiology of MetS. Activation of the NLRP3 inflammasome in adipose tissue stimulates the secretion of pro-inflammatory adipokines, such as monocyte chemoattractant protein 1 (MCP1), tumour necrosis factor (TNF), transforming growth factor-β (TGFβ), plasminogen activator inhibitor 1 (PAI1) and IL-6 (ref. 116). By contrast, the release of anti-inflammatory adipokines, such as adiponectin, is reduced by activation of the inflammasome. Accumulation of lipotoxic lipids (such as ceramides) in liver, muscle, pancreatic islets or cardiomyocytes is also associated with metabolic alterations. Studies in mice have shown that overexpression of adipose tissue or hepatic adiponectin receptors decreases intrahepatic ceramides, but also induces IR in liver and muscle[117], probably through the increase in ceramidase activity[118]. However, as a marker of abdominal obesity, a large WC is commonly associated with elevated serum levels of inflammatory markers. Therefore, measuring WC in clinical practice might be sufficient to capture a key driver of inflammation in MetS.

Infiltration of adipose tissues by immune cells and the resulting pro-inflammatory cytokine secretory profile are also well-known aspects of adipose tissue dysfunction and IR, but a detailed description is beyond the scope of this Primer. In a 2020 study that utilized single-cell RNA sequencing of VAT and SAT biopsy samples obtained from individuals with severe obesity, 17 different adipose-resident immune cell types were identified[119]. These adipose infiltrating cells relate to, and might actually contribute to IR, although most studies addressing causality were performed in animal models. Yet this chronic, low-grade inflammatory state has been shown to alter many aspects of adipose tissue function, including adipogenesis, matrix remodelling and adipose tissue metabolism, which is supported by this single-cell analysis[119].

Adipose tissue remodelling. Altered extracellular matrix remodelling in adipose tissue is an important feature of adipose tissue dysfunction that also has a potential effect on adipose tissue expandability (reviewed in refs. 120,121). Excess collagen deposition causes adipose tissue fibrosis, which can be examined through the presence of large areas of collagen fibre located in certain areas of the tissue, or around individual adipocytes in strands of varying thickness (pericellular fibrosis)[122,123]. Adipose tissue pericellular fibrosis is closely related to the number of macrophages infiltrated in adipose tissue, particularly in VAT, and is also associated with features of MetS[51].

Vascular inflammation. The mechanisms underlying the presence of hypertension in MetS are complex and probably involve the presence of ectopic adipose tissue depots, such as perivascular adipose tissue[124] and perirenal adipose tissue[125]. Perivascular adipose tissue is located around coronary arteries and strong evidence indicates a bidirectional paracrine and vasocrine interaction between this depot and events in the vascular wall involving vascular inflammation[126]. Perirenal adipose tissue also has a crucial role by increasing physical renal compression, renal sympathetic nerve activity, and angiotensin II and aldosterone secretion, as well as inducing a deficiency of natriuretic hormones and causing glucolipotoxicity through inflammation and substrate excess (reviewed in ref. 127). Perivascular adipose tissue might also modulate plaque vulnerability through its effects on the vascular wall, but many of its biological features could in turn be affected by events in the vascular wall[126,128]. Vulnerable plaques can progress to thrombosis in the milieu created by MetS, the most frequent causes being plaque rupture and erosion (reviewed in ref. 128).

Summary and the CKM syndrome concept

Collectively, adipose tissue dysfunction has a critical role in the aetiology of MetS, which manifests through reduced adipogenesis, adipocyte hypertrophy, reduced triglyceride synthesis, poor inhibition of lipolysis by insulin, immune cell infiltration, inflammatory cytokine secretion and altered adipose tissue extracellular matrix. Such a dysfunctional state reflects but also drives the accumulation of ectopic adipose tissue, a major determinant of systemic and hepatic IR and the related metabolic alterations which affect both lipid and glucose metabolism (Fig. 2). Obesity and IR in MetS have harmful effects on the vascular system, thereby predisposing people to endothelial dysfunction, arterial stiffness and vascular resistance, leading to hypertension[129], which results in the development of atherosclerosis and plaque formation[130,131]. Atherogenic dyslipidaemia, inflammatory cytokines, ROS and immune cells are also involved in formation of atheromatous plaques[132–135].

This concept was highlighted in 2023 in the AHA's Presidential Advisory[136] and Scientific Statement[12] on CKM syndrome, emphasizing the importance of a holistic approach to managing the interrelated risk factors of MetS, diabetes mellitus, CKD and CVD due to excess and/or dysfunctional adiposity. The interplay among MetS, diabetes mellitus and excess and/or dysfunctional adiposity is central to the newly developed construct of CKM syndrome, which is characterized by the central milieu of inflammation, endothelial dysfunction, oxidative stress and IR[136]. Further potentiated by the development of MASLD as described above, these key mechanisms exacerbate pathophysiological processes involved in direct vascular, myocardial and kidney injury[12]. Additional multi-organ crosstalk (such as cardiorenal interactions), with concomitant perturbations across haemodynamic and neurohormonal axes (such as the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS)) are also a hallmark of CKM syndrome[137]. Ultimately, the multidirectional interactions in CKM syndrome that largely occur downstream from excess and/or dysfunctional adiposity result in excess morbidity and mortality, which is predominantly driven by CVD, the burden of which exceeds the simple sum of its components. This risk is further amplified by adverse social determinants of health, which are influenced by the interconnectedness of genetic, biological, environmental and social risk.

Diagnosis, screening and prevention

Definition and diagnostic criteria

A clear definition of MetS is crucially important to enable prompt identification of affected patients (including with population-based tools such as electronic medical record screening), assessment of both biological and social determinants of MetS and classification into a MetS staging rubric with guideline-directed, actionable recommendations for comprehensive care. The past three decades have seen great debate over what term most precisely defines MetS, to articulate its adverse cardiovascular and metabolic effects (Table 1). Terms for MetS have continued to evolve, each focused around varying aspects of its pathophysiology, and have included syndrome X[4], the dysmetabolic syndrome[138], IR syndrome[138] and cardiometabolic syndrome. Another position, such as that adopted by the International Chair on Cardiometabolic Risk, has been to emphasize that excess VAT and/or ectopic adipose tissue underpins most forms of MetS[139]. In 2009, several major organizations released a statement harmonizing the criteria for MetS, which is currently used today[10] and the International Classification of Diseases (ICD) 10 coding terminology has adopted the current terminology of metabolic syndrome (E88.81).

These definitions are organized around the concepts that: first, MetS is a chronic and progressive pathophysiological state; second, MetS represents a clustering of risk factors that form a complex syndrome defined by a unifying pathophysiology; and third, MetS is associated with increased risk of CVD, T2DM and other related disorders. Importantly, MetS is not just a repackaging of its individual risk components, but is rather a clinical entity associated with an increased risk of CVD or death, even after controlling for its component risk factors, as seen in at least one analysis (relative risk 1.54, 95% CI 1.32–1.79)[140]. Furthermore, MetS incorporates so-called residual risk markers that are associated with CVD and metabolic disease risk, but are not universally agreed upon as criteria for MetS diagnosis; these include elevated serum levels of apolipoprotein B and small, dense LDL particles; a prothrombotic and pro-inflammatory state signified by high levels of circulating inflammatory markers (such as C-reactive protein and fibrinogen); and microalbuminuria[15]. Recognizing this construct is important, as it provides an opportunity to identify and treat residual risk markers beyond the standard management of established risk factors for CVD.

Clinical manifestations

All five clinical criteria used to diagnose MetS (WC, blood pressure, serum levels of HDL cholesterol and triglycerides, and fasting levels of blood glucose) (Table 1) can be easily and reproducibly measured in clinical practice. A comprehensive but simple framework has been developed that can be used to identify the clinical manifestations of MetS and its consequences on target organs in order to apply evidence-based, targeted therapeutic interventions (Fig. 3). This framework starts by recognizing individuals who are at risk of MetS, but without any of the five criteria required to meet a MetS diagnosis (stage A). Therapeutic interventions can be implemented to address specific health behaviours or markers of susceptibility to prevent progression (primary prevention). The model then moves towards increasingly severe stages of MetS (stages B–D) on the basis of established risk factors and diagnostic criteria, and residual risk markers. Each of these stages proposes more intensive therapeutic strategies to treat MetS and its risk factors. Of note, the risk of adverse outcomes generally increases with each subsequent stage; however, the absolute risk of developing MetS consequences varies substantially within populations. Thus, treatment decisions must be incorporated within the context of absolute risk.

A concept essential to this framework is that people with MetS have or are at risk of end-organ damage to multiple organs. This damage includes, but is not limited to, cardiovascular (atherosclerosis and non-atherosclerosis types), metabolic (for example, T2DM, dyslipidaemia and MASLD), hormonal (for example, polycystic ovarian syndrome), sleep disordered breathing, certain malignancies (for example, gastrointestinal malignancy), psychological distress (for example, depression), CKD and orthopaedic and/or joint diseases[90]. The substantial variability seen in end-organ consequences emphasizes a need to identify subtypes of MetS on the basis of their underlying pathophysiology and predisposition to adverse consequences. Different subtypes can then be targeted for specific preventive and therapeutic management strategies[11].

Emerging methods that use a personalized medicine approach to identify clinical manifestations of MetS in their early stages include: the use of novel imaging techniques to quantify the amount and quality of VAT and ectopic adipose tissue[139,141]; and the use of genetic risk scores for screening and prognostication of MetS. However, in one study[142], a polygenic risk score developed from a genome-wide association study

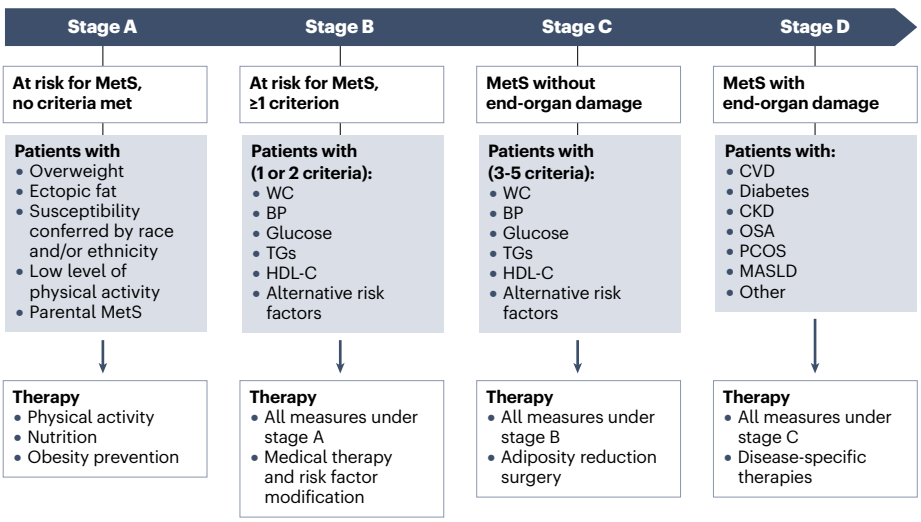

Fig. 3 | Stages in the evolution of MetS and recommended therapy by stage. This staging system highlights the progressive nature of the metabolic syndrome (MetS), with suggested criteria and recommended therapy for each stage. All therapeutic decisions should be made within the context of absolute risk for end-organ damage. BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; HDL-C, HDL cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; OSA, obstructive sleep apnoea; PCOS, polycystic ovarian syndrome; TGs, triglycerides; WC, waist circumference. Reprinted with permission from ref. 11, Elsevier.

in MetS predicted only 5.9% of the variance in MetS. Furthermore, 53 (22.5%) of the MetS-associated loci overlapped with loci that were associated with two or more MetS components. These findings indicate that MetS is a very complex, heterogeneous disorder and a single dominant genetic factor for predicting MetS might not exist.

Screening

Screening for MetS components is suggested across the life course to enhance approaches to prevention and management in both youth and adults, with the frequency and intensity of the suggested screening linked to the MetS stage (Fig. 3). In adults, at a minimum, screening should include measurement of BMI and WC at least annually, with screening for MetS components (elevated blood pressure, elevated serum levels of triglycerides, low levels of HDL cholesterol and hyperglycaemia) annually in those with existing risk factors to ensure targets are met, every 2–3 years in those living with overweight or obesity but without other risk factors, and every 3–5 years in individuals without any risk factors[136]. This approach to screening facilitates the identification of individuals at different levels of syndromic severity, thereby providing windows for preventive action to halt or reverse disease progression. A novel screening approach in development is to use artificial intelligence (AI) to find patterns in large datasets to identify individuals as at risk of or with MetS. Several studies have demonstrated feasibility in using AI to screen for MetS in both adults[143] and adolescents[144] using a variety of AI techniques.

Race/ethnicity

As discussed, the primary driver of MetS is accumulation of lipids and adipose tissue in the abdominal cavity in the form of VAT and other organs which are not physiological storage compartments for lipids (ectopic fat). Several factors, both modifiable and non-modifiable, are associated with excess VAT and MetS.

Race/ethnicity-based differences in VAT are well known and have important clinical implications for classification and risk assessment of obesity and MetS. For example, Asian American individuals, in particular South Asian people, have been observed to manifest T2DM at lower BMI levels compared with white individuals[145]. This finding could be explained in part by race/ethnicity-associated differences in visceral adiposity even when adjusted for differences in body composition. These observations have led the IDF to recommend race/ethnicity-specific cut-off values for WC in the diagnosis of MetS (Table 2). However, WC data for many populations are either unavailable or not appropriately assessed, which has led to a knowledge gap as to what specific WC cut-off values should be used to meet criteria for MetS in these populations. In a North American cohort, Black individuals were less likely to have visceral obesity and more likely to have increased lipolytic activity and show more efficient clearance of dietary triglycerides compared with white individuals[146]. Nevertheless, the relationships between visceral adiposity and adverse cardiometabolic traits persist in Black individuals.

Prevention through lifestyle patterns

Lifestyle, referring to physical activity and nutrition, is a modifiable factor that interacts with genetic susceptibility, and a healthy lifestyle is crucial to prevent and treat MetS and its consequences. Many observational studies of study populations across the world have shown an association between increased levels of physical activity and decreased rates of chronic diseases and increased longevity[147]. Even in the presence of MetS, findings from a Europe-wide study indicated that increased physical activity is associated with a substantially decreased risk of CVD[148]. The proposed mechanisms include beneficial effects on blood pressure and serum levels of lipids, which are key components of MetS.

Appropriate nutritional choices can also modify the risk of cardiometabolic disease. The Strong Heart Study, an epidemiological study of CVD in American Indian individuals identified specific dietary patterns associated with improved health outcomes[149]. Several dietary patterns, such as the dietary approaches to stop hypertension (known as DASH) and Mediterranean diets, which focus on whole grains, low-fat dairy products, legumes, nuts and olive oil, can reduce blood pressure, improve the blood lipid profile, reduce inflammation and reduce the risk of CVD[150]. Emphasis should be placed on dietary patterns, rather than specific macronutrients, given inconclusive evidence to date for an independent effect of macronutrient composition on outcomes[151]. Emerging from these data is the belief that focused research and improved education on lifestyle interventions should be prioritized for MetS prevention and treatment.

Management

Given the growing prevalence of MetS and its high likelihood of being present in most adults with obesity, the optimal management of MetS is an important clinical and public health priority. A key paradigm in the management of MetS is the importance of addressing both the diagnostic components of MetS and its additional pathophysiological features. Several systemic abnormalities that contribute to risk of end-organ damage in MetS, such as inflammation, endothelial dysfunction, a prothrombotic state and an excess of circulating small, dense LDL particles as well as abdominal obesity and hepatic steatosis, are not routinely measured in clinical practice, nor are they directly targeted by existing pharmacological therapies[152]. Therefore, fully addressing risk related to MetS involves lifestyle modification to address its root causes, including sedentary lifestyle and a lack of physical activity, excess calorie intake and an energy-dense diet of overall poor quality, and excess or dysfunctional adipose tissue, in addition to targeted pharmacotherapy to ensure optimal control of major modifiable risk factors (Fig. 4).

The importance of addressing excess or dysfunctional adiposity

The concept of MetS has been quite useful to better discriminate the heterogeneity of health risk among individuals with obesity. For example, patients with obesity without MetS have been consistently reported to be at lower risk of various cardiovascular and other health outcomes than patients with obesity with MetS. The Lancet Commission on the Definition and Diagnosis of Clinical Obesity[153] and The European Association for the Study of Obesity[154] have produced statements related to the diagnosis, staging and management of obesity in adults, which both recognize the remarkable heterogeneity of obesity. In that context, a clinical diagnosis of MetS is certainly relevant to discriminate risk early in asymptomatic individuals with obesity.

Weight reduction. Addressing obesity, particularly visceral adiposity, is one of the most important therapeutic options for MetS. Weight loss from lifestyle modification, pharmacotherapy and bariatric surgery (also known as metabolic surgery) have each been shown to improve the diagnostic components of MetS, as well as related pathophysiological features, in a weight-loss dependent manner[155–157]. In particular, both observational studies and clinical trials have shown metabolic surgery to result in sustained weight loss (20–30%), T2DM remission

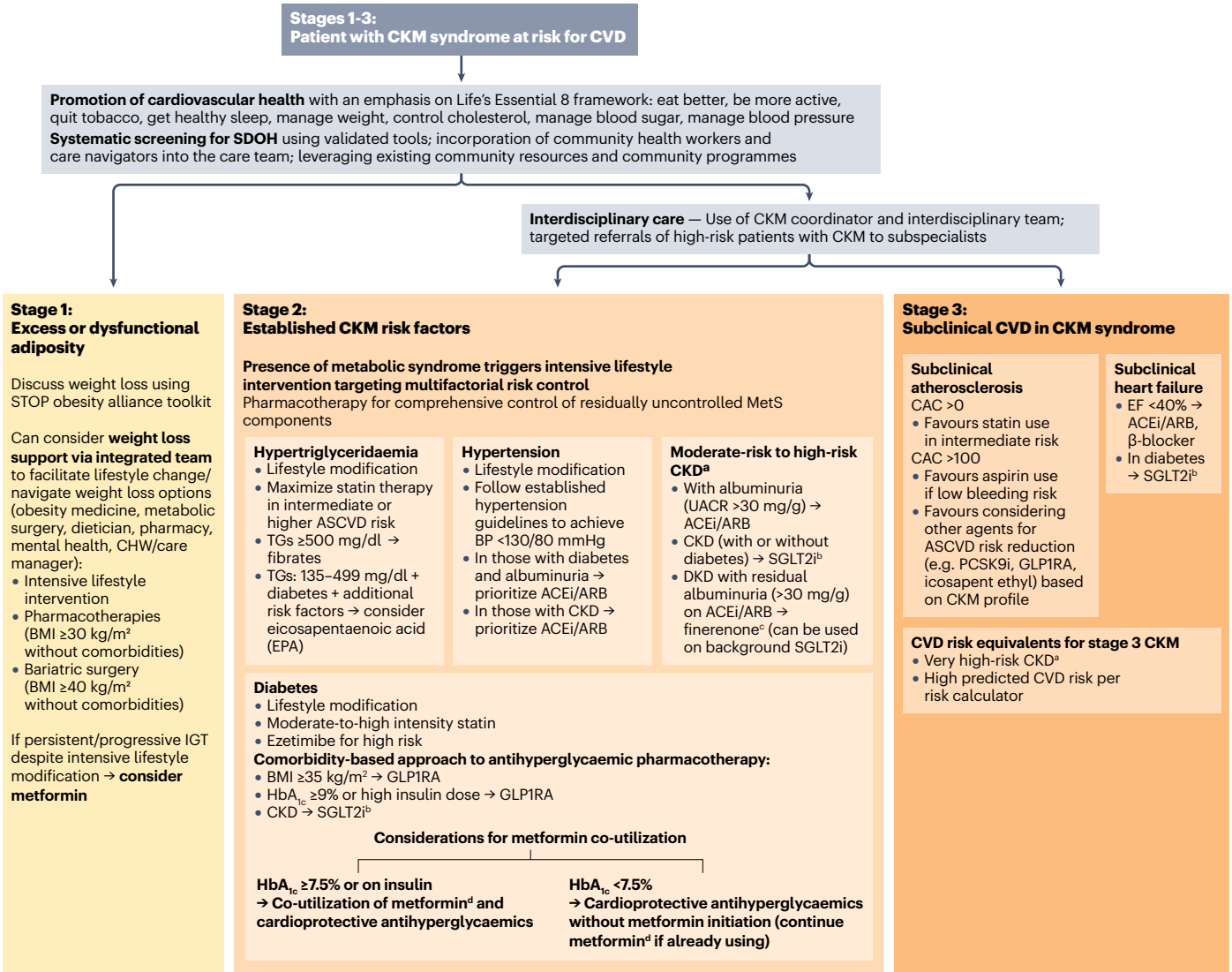

Fig. 4 | Algorithm for the management of patients with CKM syndrome stages 1–3. The American Heart Association illustrates the progressive risk of adverse cardiovascular events with advancing cardiovascular–kidney–metabolic (CKM) syndrome[136]. In stage 0, individuals have normal weight, blood glucose levels, blood pressure, lipid profiles and kidney function, and no cardiovascular disease (CVD); therefore the focus is on prevention. Stage 1 includes individuals with excess or dysfunctional adiposity, such as abdominal obesity or impaired glucose tolerance. Stage 2 includes individuals with metabolic risk factors (for example, hypertension, type 2 diabetes mellitus), moderate-to-high risk chronic kidney disease (CKD), or both. Stage 3 includes individuals with subclinical CVD alongside CKM syndrome risk factors (such as excess and/or dysfunctional adiposity, metabolic risk factors or CKD), or those with very high-risk CKD or high predicted cardiovascular risk using the AHA PREVENT risk calculator[216]. Stage 4 includes individuals with clinical CVD (for example, coronary heart disease or heart failure), further stratified by kidney failure and the need for replacement therapies. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CHW, community health worker; DKD, diabetic kidney disease; EF, ejection fraction; GLP1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, haemoglobin A_{1c}; IGT, impaired glucose tolerance; MetS, metabolic syndrome; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SDOH, social determinants of health; SGLT2i, sodium–glucose transport protein 2 inhibitors; STOP, Strategies to Overcome and Prevent; TGs, triglycerides; UACR, urine albumin–creatinine ratio. [a]Per Kidney Disease Improving Global Outcomes heat map. [b]SGLT2i can be safely initiated in patients with estimated glomerular filtration rate (eGFR) ≥20 ml/min per 1.73 m^2. [c]Finerenone can be initiated on background SGLT2i in those with eGFR >25 ml/min per 1.73 m^2 and potassium <5 mEq/l. [d]Metformin can also be used in patients with eGFR ≥30 ml/min per 1.73 m^2. Reprinted with permission from ref. 136, American Heart Association.

rates ranging from 23% to 60%, improvements in cardiovascular risk factors, such as hypertension and dyslipidaemia, and reductions in incident and recurrent cardiovascular events and mortality. Additionally, clinical trials of novel anti-obesity medications (AOMs) have shown 15–20% weight loss and improvements in multiple CVD risk factors, as well as reductions in major cardiovascular events and cardiovascular mortality[158]. Metabolic surgery can also be cost-effective and is fairly safe, with perioperative risks and mortality similar to those

of low-risk procedures such as cholecystectomy, hysterectomy and appendectomy[159,160].

Health-care professionals should adopt a non-judgemental approach when initiating weight loss discussions, as this strategy is associated with the greatest likelihood of successful weight loss attempts. A toolkit provided by the STOP Obesity Alliance, provides a helpful framework for approaching weight loss discussions, with emphasis on the 'six As': ask, assess, advise, agree, assist and arrange[161]. Given the availability of multiple modalities to facilitate weight loss, integrated weight management teams can help support a patient-centred approach to addressing overweight and obesity. According to the CKM syndrome health guidance, the use of such a team should be prioritized for individuals with existing CVD or at high risk of CVD owing to multiple comorbid conditions[136].

Lifestyle interventions

Lifestyle modification in MetS is focused on behaviour change to support sustained beneficial lifestyle practices, such as improving overall dietary patterns (DASH or Mediterranean-type diets), moderate calorie restriction and regular physical activity[162]. Lifestyle modification is best achieved through structured, multidisciplinary programmes with ongoing support to facilitate sustained behaviour change[163].

Diet. From a dietary standpoint, key elements include a balanced diet with limited intake of simple carbohydrates and saturated fat, and increased intake of lean proteins, whole-grains, fruits, vegetables and ω-3 fatty acids[164]. The Mediterranean diet, the DASH diet and high-fibre diets each improve multiple aspects of MetS. The Mediterranean diet demonstrates particularly potent anti-inflammatory effects and the DASH diet has a notable effect on reducing blood pressure. In those with excess adiposity, moderate calorie restriction of 500–1,000 kcal per day can promote reductions in weight and adipose tissue mass[165]. However, even in the absence of weight and adipose tissue mass loss, dietary interventions can have substantial benefits in reducing the risk of CVD. The PREDIMED trial, which tested the Mediterranean diet in patients with MetS with and without diabetes mellitus, was aimed at improving overall diet quality rather than weight loss and showed a 28–31% relative risk reduction in the composite CVD end point[150].

Physical activity. Physical activity has a substantial positive effect on MetS. In randomized trials of heterogeneous populations, aerobic physical activity improved each of the diagnostic components of MetS and additional pathophysiological features, such as inflammation and endothelial dysfunction[166]. Furthermore, the addition of resistance training to aerobic activity is linked to further improvements in MetS components and is therefore advised as part of the exercise regimen[167]. In general, moderate to vigorous physical activity on most days of the week is recommended, with a goal of 150 min or more of physical activity per week[168]. While weight loss with lifestyle modification is desirable, patients and health-care professionals must recognize that improved dietary patterns and regular physical activity improve MetS independent of weight loss[155].

Other aspects of lifestyle modifications. One important part of the approach to lifestyle modification is to screen for adverse social determinants of health that affect lifestyle behaviours, and to provide social support where needed through community health workers, care navigators or social workers[169]. Adequate sleep and stress management also have a favourable effect on the likelihood of engaging in healthy lifestyle behaviours, and should be advised for patients with MetS. Given the increased risk of atherothrombosis in MetS, smoking cessation in this patient population is particularly key to emphasize, as a key aspect of healthy lifestyle practices. In addition to lifestyle modification, moderation of alcohol use should be advised to lessen the risk of hepatic complications.

Targeted pharmacotherapy

In the management of MetS, lifestyle modification should be accompanied by targeted pharmacotherapy for optimal cardiovascular risk reduction (Table 3 and Fig. 4). In the STENO-2 randomized trial in 160 patients with overweight or obesity, T2DM and albuminuria, standard care was compared with a multifactorial intervention including lifestyle modification, glycaemic control, RAAS inhibition, aspirin and lipid-lowering therapy[170]. Over a mean 5 years of follow-up, those individuals who received the multifactorial intervention had a 46% lower risk of death, a 57% lower risk of cardiovascular death, and a 59% lower risk of cardiovascular events. These findings highlight the clinical benefit of combining lifestyle change with pharmacotherapies known to control risk factors and reduce cardiovascular risk in individuals with MetS. Also of relevance is that heterogeneity exists among individuals with MetS, with individuals having IR-dominant, lipid-dominant and vascular-dominant phenotypes[11]. Pharmacotherapy should therefore be targeted towards addressing these overt risk factor abnormalities to customize approaches for cardiovascular risk reduction.

T2DM. MetS confers up to a fivefold higher risk of developing T2DM and the majority of individuals with T2DM have concurrent MetS[171]. MetS traits also increase the risk of major adverse liver outcomes in patients with T2DM[172]. The Diabetes Prevention Program trial demonstrated that lifestyle modification is a highly effective strategy for preventing the development of diabetes mellitus[173]. Metformin is also effective for T2DM prevention, although less so than lifestyle modification, and can be considered for those with progressive hyperglycaemia despite lifestyle changes. If T2DM develops, lifestyle modification should be accompanied by moderate-intensity to high-intensity statin therapy for LDL cholesterol lowering, and glycaemic control with haemoglobin A_{1c} of <7% to prevent microvascular complications. Established anti-hyperglycaemic medications that have shown benefit in MetS include insulin sensitizers (metformin and thiazolidinediones, such as pioglitazone). Additionally, modern anti-diabetic agents such as glucagon-like peptide 1 (GLP1) receptor agonists (Box 1) and sodium–glucose cotransporter 2 (SGLT2) inhibitors (Fig. 5) improve cardiovascular outcomes in several subgroups of patients at high cardiovascular risk with and without T2DM[174–177]. Novel dual GLP1–glucose-dependent insulinotropic polypeptide (GIP) receptor agonists and triple (GLP1–GIP–glucagon) receptor agonists have also been proven to have cardiometabolic benefits among individuals with overweight or obesity and diabetes mellitus[178–181]. Common adverse effects with SGLT2 inhibitors include genital mycotic infection and volume depletion, and those with GLP1 and related receptor agonists include gastrointestinal issues, such as nausea, vomiting and constipation.

Hypertension. Hypertension is a diagnostic component of MetS, and blood pressure reduction confers marked reduction in cardiovascular risk in individuals with or at risk of CVD[182]. Major societies have agreed

Table 3 | Candidate therapeutic agents for metabolic syndrome and its components

Therapy	MetS component					Other factors		Strengths	Limitations or caveats	Medications
	Abdominal obesity	Glucose or IR	TGs	HDL-C	BP	Inflammation (CRP)	Hepatic steatosis			
GLP1RA or GLP1-based therapy	↓↓	↓↓	↓↓	↑	↓	↓	↓↓	CV benefits mainly in ASCVD; kidney benefits	GI adverse events	Liraglutide, exenatide, lixicenatide, dulaglutide, efpeglenitide, semaglutide, tirzepatide, orforglipron[a], survodutide[a], retatrutide[a], cafraglutide[a]
SGLT2i	↓	↓	↓	↑	↓	↓	↓	CV benefits mainly in HF; kidney benefits	↑ Genital tract infection; volume depletion; ketosis	Dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, enavogliflozin
DPP4i	–	↓	↓	–	–	↓	–	Albuminuria reduction	↑ HF risk in saxagliptin	Sitagliptin, vildagliptin, linagliptin, alogliptin, saxagliptin, teneligliptin, gemigliptin, anagliptin, evogliptin
TZD	↑[b]	↓↓	↓↓	↑	–	↓	↓↓	CV benefits, mainly in stroke	↑ HF risk; ↑ osteoporosis risk	Pioglitazone, rosiglitazone, lobeglitazone
Statins	–	Slightly ↑	↓	–	–	↓	–	CV benefits	Muscle-related side effects; glucose dysregulation; ↑ LFT	Atorvastatin, rosuvastatin, simvastatin, fluvastatin, pravastatin, lovastatin, pitavastatin
Fibrates	–	Slightly ↓	↓↓	↑	–	↓	–	↓ Diabetic microvascular complications	Transient ↓ eGFR	Fenofibrate, gemfibrozil
EPA	–	Slightly ↓	↓↓	↑	–	↓	↓	CV benefits	Atrial fibrillation at high dose; GI adverse events	Icosapent ethyl
ARB or ACEi	–	Slightly ↓	–	–	↓↓	↓	–	CV benefits; kidney benefits	Cough with ACEi	Losartan, candesartan, telmisartan, irbesartan, eprosartan, fimasartan, olmesartan, azilsartan

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CRP, C-reactive protein; CV, cardiovascular; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; GI, gastrointestinal; GLP1, glucagon-like peptide 1; GLP1RA, GLP1 receptor agonist; HDL-C, HDL cholesterol; HF, heart failure; IR, insulin resistance; LFT, liver function test; MetS, the metabolic syndrome; SGLT2i, sodium–glucose cotransporter 2 inhibitors; TGs, triglycerides; TZD, thiazolidinedione. [a]Not yet approved for obesity or diabetes management by the FDA or EMA, or in other countries. [b]Mainly subcutaneous adipose tissue.

that a blood pressure goal of <130/80 mmHg should be targeted with lifestyle modifications, a low sodium diet and pharmacological therapy for individuals who are at increased risk[183]. From a dietary standpoint, the DASH diet is associated with notable lowering of blood pressure. From a pharmacological standpoint, the use of diuretics, calcium channel blockers or RAAS inhibitors as pharmacological agents to reduce blood pressure confer similar cardiovascular benefits in most patients with MetS. However, RAAS inhibitors should be prioritized in patients with CKD, diabetes mellitus with albuminuria and existing CVD (particularly heart failure), to confer additional risk reduction against adverse kidney and cardiovascular events[12].

Dyslipidaemia. Atherogenic dyslipidaemia, characterized by the interrelated lipid phenotypes of elevated blood levels of triglycerides, low HDL cholesterol, elevated apolipoprotein B (or non-HDL cholesterol) and an increased proportion of small, dense LDL particles, is closely related to IR, and is therefore commonly encountered in patients with MetS. Genetic studies have demonstrated a causal relationship between elevated triglycerides and CVD, in contrast to low HDL cholesterol, which is now appreciated as a marker of metabolic dysregulation. In the absence of secondary causes for elevated triglycerides, lifestyle modification is the first-line therapy for hypertriglyceridaemia in the context of MetS. In those with CVD or intermediate-to-high predicted risk, statin therapy is indicated and has a moderate triglyceride-lowering effect. Icosapent ethyl can be considered to further reduce CVD risk in those with elevated triglycerides concomitant with CVD or with diabetes mellitus in addition to other risk factors[184].

High potency statins might slightly increase the risk of incident T2DM in those with prediabetes. The number needed to be treated to harm one individual is ~100, so individuals with a predicted CVD risk exceeding 2.5% over 10 years derive more benefit than potential harm from statin use. Aspirin should be used infrequently in the routine primary prevention of CVD related to MetS owing to a lack of net benefit[185–187]. Current guidelines from the American College of

Cardiology–AHA recommend that low-dose aspirin (75–100 mg orally daily) be considered for the primary prevention of CVD among selected adults aged 40 to 70 years who are at increased risk of CVD but not at increased risk of bleeding (class IIb recommendation)[183].

Chronic kidney disease. CKD is a frequent consequence of MetS, reflecting the adverse effects of obesity, inflammation, IR, T2DM and elevated blood pressure. In individuals with MetS, the health guidance for CKM syndrome emphasizes the measurement of the urine albumin-to-creatinine ratio and estimated glomerular filtration rate to fully characterize CKD-related risk[136]. Therapies to prevent kidney function decline should be prioritized in individuals with CKD. RAAS inhibitors are proven to reduce adverse kidney events in individuals with CKD with albuminuria[188]. Furthermore, SGLT2 inhibitors are now known to reduce adverse kidney events in most individuals with CKD, even in the absence of diabetes mellitus or albuminuria[189,190]. In addition, the non-steroidal mineralocorticoid receptor antagonist finerenone reduces adverse kidney events in individuals with diabetic CKD[191]. In patients with CKD and T2DM, treatment with the GLP1 receptor agonist semaglutide improved kidney outcomes[192]. Importantly, these kidney-protective agents also have favourable effects on cardiovascular outcomes (especially heart failure), which are mediated in part by protection against kidney function decline. The Effects of Semaglutide on Chronic Kidney Disease in Type 2 Diabetes (FLOW) trial is the first kidney outcomes trial of GLP1 receptor agonists that demonstrated significant reductions in the rates of adverse kidney events and death from cardiovascular causes in individuals with T2DM and CKD with semaglutide compared with placebo (HR 0.76, 95% CI 0.66–0.88)[193]. The FLOW trial also notably showed a 20% reduction in rates of death from all causes in this high-risk patient population.

Box 1 | The potential role of GLP1RA or GLP1–GIP dual agonists in glucose and lipid metabolism and cardiorenal systems

Glucose and lipid metabolism

- ↓ Insulin resistance
- ↓ Glucose and glycated haemoglobin
- ↓ Body weight and WC
- ↓ Visceral adipose tissue
- ↓ Hepatic steatosis and MASLD
- ↓ Pericardial adipose tissue
- ↓ Triglycerides and VLDL
- ↓ LDL cholesterol and sdLDL
- ↑ HDL cholesterol

Cardiorenal systems

- ↓ Blood pressure
- ↑ Endothelial function
- ↑ Cardiac function
- ↓ Cardiac ischaemia
- ↓ Atherosclerosis
- ↓ Albuminuria

Shared pathways

- ↓ Inflammation
- ↓ Oxidative stress
- ↑ Adiponectin

GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide 1; GLP1RA, GLP1 receptor agonist; MASLD, metabolic dysfunction-associated steatotic liver disease; sdLDL, small dense LDL; WC, waist circumference.

Management in children and adolescents

MetS in children and adolescents is a frequently discussed topic in the literature, yet uniform guidelines on its definition and treatment are still lacking[28]. As in adults, IR, central obesity, dyslipidaemia and hypertension are commonly considered as the main components of MetS in children and adolescents. The first recommended approach to all these pathological conditions in these groups is lifestyle intervention (that is, weight management, diet and physical activity)[193,194]. However, in selected patients at very high risk, a pharmacological or surgical treatment might prove useful for the prevention of metabolic and cardiovascular complications[193,194].

Quality of life

MetS has considerable potential to affect multiple domains of a patient's health-related quality of life (HRQOL): psychosocial, emotional and physical[195,196]. This issue is particularly relevant, as self-perceived HRQOL is suggested to be an important predictor of chronic disease development and premature mortality[197]. For example, in several cross-sectional studies, MetS was found to be associated with increased prevalence of depressive symptoms and adverse mental health QOL, particularly in women[198,199] and those from lower socioeconomic backgrounds[198]. In an 8-year prospective cohort study that followed middle-aged adults (aged 35–55 years) in Taiwan, after adjusting for physical activity, MetS was a strong risk factor for negative psychological well-being, particularly in relation to vitality and overall mental health[196]. The syndrome also predisposes individuals to bodily pain and can limit physical activity[197,200], which might impede the ability to lose excess body weight and can further compound the negative effects on HRQOL[200].

As MetS encompasses a cluster of cardiometabolic risk factors, it is implicated in increased rates of morbidity and mortality across the lifespan[198,201]. These increases are due in part to associations with cognitive and functional decline and poor perception of health, as well as to increased rates of cerebrovascular disease and CVD[198,199]. In a study including populations historically under-represented in research in the USA, MetS was linked to reduced HRQOL among non-Hispanic white individuals, non-Hispanic Black individuals and Mexican Americans[201]. Notably, the findings were variable across studies, as some showed no differences in HRQOL domains (such as depressive symptoms) between those with and without MetS[202]. Future studies including patients from diverse backgrounds[196], of all age groups and with standardized measurements for HRQOL and MetS[200], are needed to better elucidate the independent effect of MetS on HRQOL.

Primary treatment recommendations typically involve lifestyle modifications, including exercise[203], yoga[204], nutrition health education[205] and health behaviour changes[206]. In a randomized controlled trial exploring the effects of lifestyle changes on MetS management, lifestyle modification significantly improved the physical health domain of HRQOL at 3 months ($P = 0.02$)[203]. These findings were bolstered in a meta-analysis of such interventions, which highlighted the value of healthy lifestyle modifications on all HRQOL domains[203–206]. In addition, one unique population comprises patients who develop

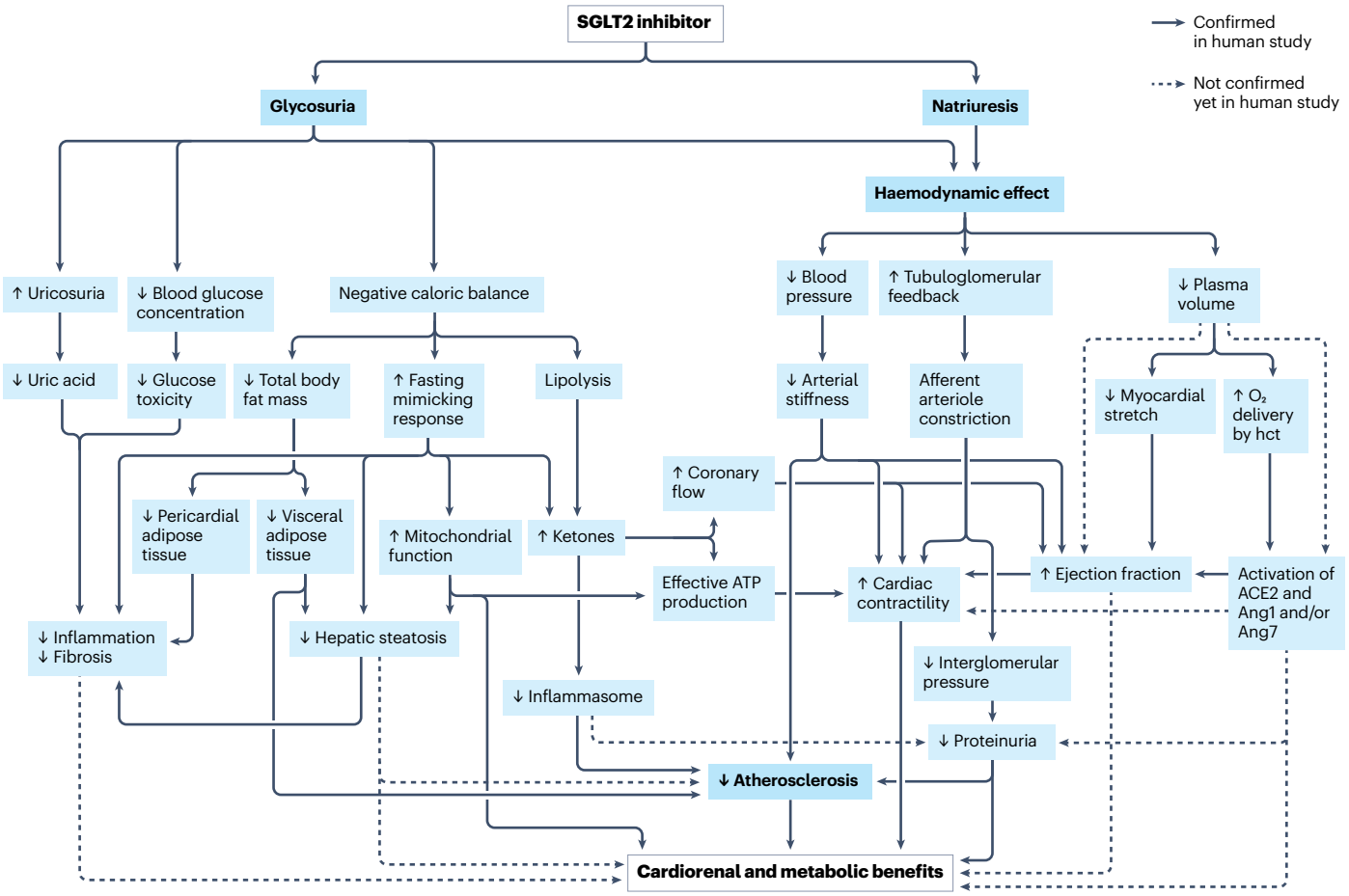

Fig. 5 | The potential mechanisms of SGLT2 inhibitors leading to cardiorenal and metabolic benefits. Sodium–glucose cotransporter 2 (SGLT2) inhibitors exert cardiorenal and metabolic benefits through multifaceted mechanisms. SGLT2 inhibitors promote glycosuria, leading to a reduction in blood glucose levels and a negative caloric balance. These effects contribute to decreased uric acid levels, reduced glucose toxicity and decreased total body fat mass, particularly visceral and pericardial adipose tissue, while enhancing mitochondrial function and increasing ketone production. These metabolic changes are associated with decreased inflammation and fibrosis, reduced hepatic steatosis and overall cardiovascular protection. Additionally, the haemodynamic effects, including natriuresis, reduced blood pressure and plasma volume, contribute to improved renal function by decreasing tubuloglomerular feedback and interglomerular pressure. Enhanced coronary flow, reduced arterial stiffness and improved myocardial oxygen delivery further support cardiac function, evidenced by increased ejection fraction and cardiac contractility. Together, these mechanisms underscore the systemic benefits of SGLT2 inhibitors in managing cardio–renal–metabolic disorders. Solid lines: confirmed in human study. Dashed line: not confirmed yet in human study. ACE2, angiotensin-converting enzyme 2; Ang1, angiotensin 1; Ang7, angiotensin 7; hct, haematocrit.

cancer treatment-induced MetS, thereby emphasizing a need to integrate surveillance for MetS in patients with cancer, especially as part of routine survivorship health care to potentially improve HRQOL[207]. Thus, additional investigation into the relationship between MetS and HRQOL is warranted to better understand the multifaceted effects of MetS on all domains of well-being.

Outlook

Gaps between scientific evidence and implementation

Considerable evidence indicates that a clinical diagnosis of MetS can predict an increased risk of developing T2DM and CVD, as well as other clinical outcomes. Yet, several gaps exist between the science underlying MetS and implementation of MetS diagnosis and intervention in clinical practice. Importantly, health-care professionals often fail to recognize the need to assess and target abdominal obesity and its clinical consequences as early as possible. Abdominal obesity is characterized by dysfunctional and hypertrophic SAT (which is not able to expand and act as a metabolic sink) accompanied by excess VAT and ectopic lipid accumulation. Health-care professionals need to be aware that the current tool used in clinical practice to assess obesity (that is, BMI) cannot adequately assess the quality of SAT and the size of adipose tissue depots associated with features of MetS (such as visceral adiposity and hepatic steatosis). A diagnosis of MetS enables patients with overweight or obesity who are at increased risk to be identified and targeted for early intervention to prevent the development of various clinical outcomes. In addition, a MetS diagnosis should be incorporated into a proper individualized health risk assessment that considers the severity of the MetS, as well as many genetic and environmental

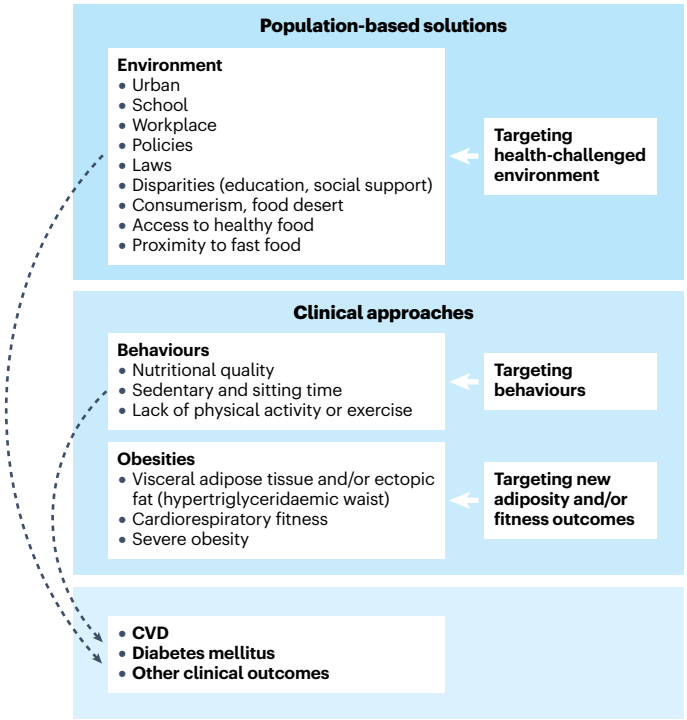

Fig. 6 | Clinical approaches and public health solutions to tackle obesities. As high-risk forms of obesity result from the complex interactions of biological, behavioural, psychosocial and environmental factors, the current obesity epidemic will not be curbed until an integrated set of population-based solutions and clinical approaches are put in place, going beyond body weight and weight loss as the single assessment or management outcome. CVD, cardiovascular disease. Reprinted with permission from ref. 208, Elsevier.

or lifestyle factors. AI approaches have tremendous potential to help address these challenges.

Clinicians also need to recognize that features of MetS result from the interaction between genetic susceptibility, family history and lifestyle factors (including, among others, overall dietary patterns, physical activity and sedentary time, and quality of sleep). These factors are also related to socioeconomic issues that often cannot be addressed by classic health-care models, as clinical treatments that target the individual and public health approaches that target populations are often in their separate silos[208] (Fig. 6). In that regard, the AHA CKM syndrome screening and staging concept published by the AHA[12] (Fig. 4) is an important conceptual step forward. This approach puts an emphasis on targeting stage 1 (high risk obesity and/or prediabetes) with specific recommendations around screening and intervention to prevent stage 2 (essentially MetS). Furthermore, this AHA presidential advisory paper[12] emphasizes the need to develop integrated models to fill the gap between clinical approaches and strategies to address social determinants of health, such as patient-centred, team-based approaches like the CINEMA programme[209].

Recognition of MetS as a distinct clinical entity

The concept of MetS was introduced >20 years ago; however, primary care providers (and many specialists) still consider the component risk factors in isolation and do not appreciate their interconnectedness nor the importance of addressing upstream drivers of the CKM syndrome with a holistic approach. Whereas clinicians familiar with the concept will 'code' MetS for these patients, too many of them still see MetS criteria such as hypertension, impaired fasting glucose and high serum levels of triglycerides, in isolation from each other and treat these risk factors in silos. Therefore, appropriately using the MetS concept for optimal assessment and management of health risk remains a challenge in clinical practice.

This situation could be partly attributed to the fact that some groups of experts have even debated about the added value of the MetS concept. MetS is not a risk calculator, and clinicians have difficulties with incorporating a MetS diagnosis into the risk assessments of their patients for various health outcomes. We propose that just assessing the metabolic and/or haemodynamic features of MetS in themselves does not make sense, until attention is paid to the key driver: dysfunctional SAT that leads to excess VAT and ectopic lipid accumulation. Thus, if a consensus can be achieved around visceral obesity with excess ectopic lipid accumulation being the most common form of MetS, approaches will need to be developed so that health professionals can diagnose visceral obesity at any BMI value. WC has been proposed as a simple marker of abdominal obesity. However, the widely used single sex-specific WC cut-off values (88 cm in women and 102 cm in men) to diagnose abdominal obesity are not sufficient because both BMI and WC are strongly correlated (Fig. 7). Rather, sex-specific and BMI category-specific WC values have been proposed[210] but these recommendations have failed to be widely implemented. Further work in this area and additional consensus activities are clearly needed.

Body adiposity imaging and cardiometabolic risk assessment

Another area of uncertainty is the role of body adiposity imaging in assessing cardiometabolic risk and the distinct contribution of excess visceral adiposity versus those of ectopic lipid depots (such as in the liver, muscle or pancreas) and the epicardial, pericardial and perirenal adipose tissue depots to various clinical outcomes. Advanced body adiposity imaging using CT or MRI (the gold standard) is not available in most centres and the cost-effectiveness of an imaging-based screening approach has not been evaluated. Dual energy X-ray absorptiometry scanning is more widely available but provides limited information. In the absence of direct, imaging-based tools such as CT and MRI for clinical use, a combination of anthropometry and laboratory markers could aid in the differentiation of high-risk adiposity phenotypes[208].

Whereas hepatic steatosis has an important role in the development of T2DM, its contribution to CVD outcomes is uncertain[100,211]. However, MASLD or MASH, rather than isolated hepatic steatosis, is associated with increased CVD risk. A meta-analysis investigated the association between MASLD (diagnosed by liver imaging, ICD codes or liver histology) in ~5.8 million middle-aged individuals from different countries with nearly 100,000 fatal and non-fatal CVD events over a median follow-up of 6.9 years, and found a hazard ratio of 1.45, but this risk markedly increased across the severity of MASLD, especially with the stage of fibrosis (pooled random effects HR 2.50)[212]. Moreover, in Sweden from 1998 to 2021, the risk of major adverse liver outcomes increased with the number of MetS traits in individuals with T2DM without a history of liver disease identified from national registers[173]. In addition, in a 2024 Korean nationwide analysis, patients with MASLD (assessed as a fatty liver index (FLI) of ≥30) and T2DM (and even those with mild MASLD (FLI 30 to <60)) had

a higher risk of CVD and all-cause death than those without MASLD (FLI <30)[213]. In a 2023 study that used the NHANES data from 1999 to 2018, assessment of MASLD led to identification a greater proportion of the population with metabolic risk[214]. Moreover, although epicardial and pericardial adipose tissue are related to CVD outcomes, their specific contribution to clinical outcomes after controlling for VAT remains debated. For instance, in a recent analysis of 44,475 participants from the UK Biobank, although epicardial and pericardial adiposity was associated with incident CVD, the association was largely explained by a metabolically unhealthy adiposity phenotype characterized by excess VAT[215].

In summary, the relative contribution of various ectopic adipose tissue depots to MetS could depend upon the clinical outcome considered. As multiple forms of ectopic adipose phenotypes are observed in the population, machine learning systems and AI will be helpful to categorize these adiposity phenotypes and their associated risk.

The role of MetS in risk stratification and personalized medicine

Another limitation of the definition of MetS is that it is an 'all or none' diagnosis (presence versus absence on the basis of meeting three out of the five clinical criteria or not). New models of CKM syndrome risk have attempted to address this issue by developing approaches to integrate lifestyle indices with biological risk factors[12]. These include the PREVENT risk calculator published by a working group with the AHA, which is a set of novel risk prediction equations that incorporate predictors and outcomes relevant to the CKM syndrome context[216]. This risk prediction tool includes an assessment of social determinants of health, which are key upstream drivers of CVD, to more equitably estimate and address risk[216]. Further work is certainly needed to properly evaluate how the severity of MetS features can be considered in overall risk assessment tools. No international consensus exists around this question.

The utilization of MetS as a risk stratification tool to target intensive interventions towards those at highest risk of adverse outcomes should be a research priority in the next 5–10 years. For example, an opportunity exists to ensure the appropriate utilization of AOMs using screening and diagnosis of MetS to focus treatment on the highest risk individuals. The prescribing of AOMs should be approached in the context of cardiometabolic risk management (atherosclerotic CVD, heart failure and T2DM) and not for weight loss alone. In particular, GLP1-based agents are effective in decreasing both abdominal VAT and hepatic steatosis[176,217–219]. An accurate assessment of MetS can assist with identifying those at highest risk and likely to derive greatest benefit from these costly agents.

Metabolic surgery is another area in which the screening and identification of MetS can help further refine risk stratification and the application of resources to target those who will benefit the most. Severe obesity is the fastest growing obesity category in the USA[220]. Progress has been made in the development of less-invasive and safer approaches (for example, laparoscopic and endoscopic procedures), making metabolic surgery a more acceptable, viable option for many patients.

In summary, the concept of MetS and simple diagnostic tools have been helpful to identify the subgroup of individuals with overweight or obesity who are at highest risk of developing various adverse clinical outcomes. Dysfunctional adipose tissue in the presence of a permissive lifestyle and environmental or socioeconomic factors drive the development of MetS; therefore, the challenge will be to develop integrated and equitable clinical and public health approaches to manage a highly prevalent condition. Public health approaches to increase physical activity and improve overall nutritional quality will be the most successful when we can translate them into improvements in defining the features of MetS and related risk. Thus, from a public policy standpoint, monitoring changes in the features of MetS and its severity could help track and measure improvements in risk factors conferred by lifestyle modification.

Finally, with the availability of costly drugs (including AOMs) and surgical procedures, a remaining challenge will be to identify the best therapeutic option for the right patient. In this regard, the recently published statement on the CKM syndrome is an important step forward to better assess, manage and even prevent this important condition[136]. Taking this prevention mindset even further, the field should add focus to not just managing MetS but rather emphasizing the promotion of 'metabolic health' to prevent the development and complications of MetS in the first place. Prevention efforts will

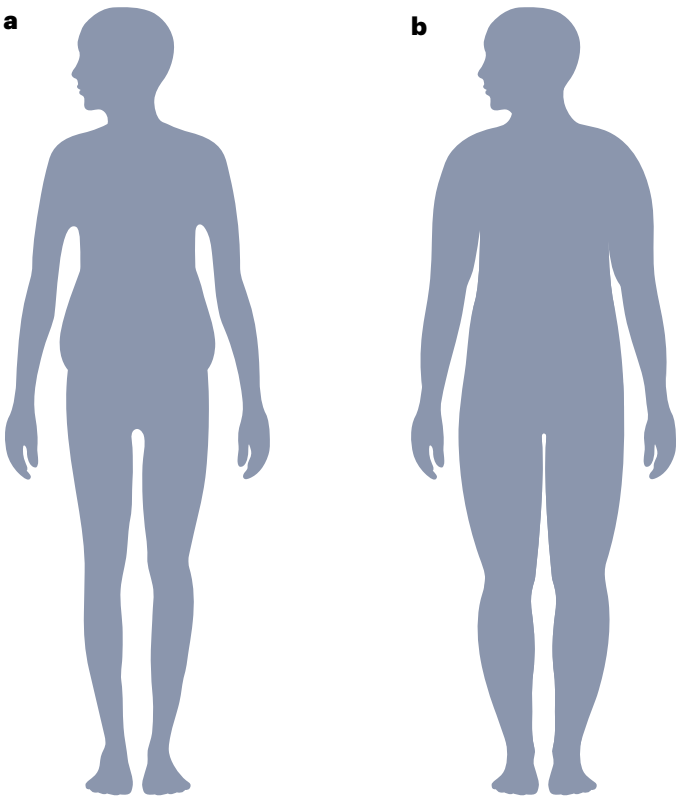

Fig. 7 | Two individuals with identical waist circumference values but markedly different body composition and adipose tissue distribution. The individual in panel **a** (individual **a**) has a waist circumference of 102 cm and a BMI of 26 kg/m^2. The individual in panel **b** (individual **b**) also has a waist circumference of 102 cm but a BMI of 32 kg/m^2. Assessing health risk only on the basis of the BMI would imply that individual **b** is at higher risk than individual **a**, which would be incorrect. However, simultaneous measurement and interpretation of both waist circumference and BMI values would reveal that individual **a** has sarcopenia and visceral obesity and should be assessed for metabolic dysfunction-associated steatotic liver disease. Individual **a** is therefore at high risk of cardiometabolic outcomes. Individual **b** has higher levels of subcutaneous adipose tissue and a greater muscle mass than individual **a**. Thus, despite having a higher BMI than individual **a**, individual **b** is at lower risk of cardiometabolic outcomes.

require individual, regional and societal efforts towards change that can set a new trajectory towards optimal metabolic health for the next generation.

Published online: 17 October 2024

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Author contributions

Introduction (all authors); Epidemiology (J.-P.D. and S.L.); Mechanisms/pathophysiology (J.-P.D., I.J.N., A.T., S.L. and A.G.); Diagnosis, screening and prevention (J.-P.D., I.J.N., A.T., A.G., J.R. and C.E.N.); Management (J.-P.D., I.J.N., A.T., S.L., J.R., C.E.N. and T.M.P.-W.); Quality of life (T.M.P.-W.); Outlook (J.-P.D., I.J.N., S.L., A.G., J.R. and T.M.P.-W.); revisions/editing of the whole manuscript (all authors).

Competing interests

I.J.N. has received honoraria, consulting and speaker's bureau fees from Boehringer Ingelheim/Lilly Alliance, consulting and speakers' bureau fees from Bayer Pharmaceuticals, and has participated in scientific advisory boards for Lilly, Boehringer Ingelheim, Novo Nordisk and AMRA Medical. S.L. has been a member on advisory boards or has consulted with Novo Nordisk, and has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Abbott, LG Chem., Daewoong Pharmaceutical, Chong Kun Dang Pharmaceutical and Novo Nordisk. A.T. receives research funding from Johnson & Johnson, Medtronics, GI Windows and Biotwin for studies on obesity and bariatric surgery, and has acted as a consultant for Bausch Health, Novo Nordisk and Biotwin. A.G. has served as a consultant for Boehringer Ingelheim, Eli Lilly and Company, Metadeq Diagnostics; has participated on advisory boards for Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Metadeq Diagnostics and Pfizer; and has received speaker's honoraria and other fees from Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk and Pfizer. J.R. is on the speakers' bureau of Boehringer Ingelheim and acts as a consultant (advisory boards) for Boehringer Ingelheim, Edwards LifeSciences, Procyrion Inc. and AstraZeneca. T.M.P.-W. is paid by the American Heart Association as an Associate Editor for *JAHA*. C.E.N. and J.-P.D. declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41572-024-00563-5.

Peer review information *Nature Reviews Disease Primers* thanks E. Rinkuniene, E. Stener-Victorin, D. Tousoulis, G. Watts and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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